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Oncogenes induce the cancer-associated fibroblast phenotype

Metabolic symbiosis and "fibroblast addiction" are new therapeutic targets for drug discovery

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Metabolic coupling, between mitochondria in cancer cells and catabolism in stromal fibroblasts, promotes tumor growth, recurrence, metastasis, and predicts anticancer drug resistance. Catabolic fibroblasts donate the necessary fuels (such as L-lactate, ketones, glutamine, other amino acids, and fatty acids) to anabolic cancer cells, to metabolize via their TCA cycle and oxidative phosphorylation (OXPHOS). This provides a simple mechanism by which metabolic energy and biomass are transferred from the host microenvironment to cancer cells. Recently, we showed that catabolic metabolism and "glycolytic reprogramming" in the tumor microenvironment are orchestrated by oncogene activation and inflammation, which originates in epithelial cancer cells. Oncogenes drive the onset of the cancer-associated fibroblast phenotype in adjacent normal fibroblasts via paracrine oxidative stress. This oncogene-induced transition to malignancy is "mirrored" by a loss of caveolin-1 (Cav-1) and an increase in MCT4 in adjacent stromal fibroblasts, functionally reflecting catabolic metabolism in the tumor microenvironment. Virtually identical findings were obtained using BRCA1-deficient breast and ovarian cancer cells. Thus, oncogene activation (RAS, NFkB, TGF-β) and/or tumor suppressor loss (BRCA1) have similar functional effects on adjacent stromal fibroblasts, initiating "metabolic symbiosis" and the cancer-associated fibroblast phenotype. New therapeutic strategies that metabolically uncouple oxidative cancer cells from their glycolytic stroma or modulate oxidative stress could be used to target this lethal subtype of cancers. Targeting "fibroblast addiction" in primary and metastatic tumor cells may expose a critical Achilles' heel, leading to disease regression in both sporadic and familial cancers.

Introduction

It is now well-established that (1) oncogene activation, and (2) aberrant growth factor signaling, are sufficient to mediate cell transformation, tumor growth, and metastasis. However, this highly simplified view of cancer does not mechanistically explain the essential role of the tumor stroma or the host cellular microenvironment.

Thus, a more integrated metabolic model of how cancer works will be required for us to invent new effective and non-toxic cancer therapies.[1–11] Toward this end, here we will focus on the metabolic-interface between cancer cells and their host microenvironment: cancer-associated fibroblasts or CAFs. We believe that catabolic cancer-associated fibroblasts are a key metabolic "fuel source", for enabling cancer cell propagation, survival, and systemic dissemination, during metastasis.

Metabolic Symbiosis: Implications for Personalized Medicine and Cancer Therapy

Recent studies directly show that cancer cells extract high-energy nutrients from cancer-associated fibroblasts or other normal adjacent cells, such as adipocytes, via oxidative stress.[12-54] This "metabolic symbiosis" would be most essential during early tumorigenesis and later during cancer cell metastasis, when a blood supply is largely absent. We also have termed this type of symbiotic or parasitic relationship "two-compartment tumor metabolism" or "the reverse Warburg effect".[31,33,40,42-45] During metabolic symbiosis, catabolic fibroblasts provide the necessary fuels (such as L-lactate, ketone bodies, glutamine, other amino acids, and free fatty acids) to anabolic cancer cells, to metabolize via their TCA cycle and oxidative phosphorylation (OXPHOS). Energy transfer occurs via a stromal–epithelial "lactate shuttle" to efficiently move nutrients from fibroblasts to tumor cells. To accomplish this energy transfer, fibroblasts excrete L-lactate and ketones using MCT4 transporters.[55,56] In contrast, tumor cells take up and re-purpose these fuels using MCT1 transporters.

Here, we discuss the use of 3 new clinical biomarkers of metabolic symbiosis for predicting patient outcome in human breast cancers and other types of cancer. These 3 biomarkers include MCT1, MCT4, and Caveolin-1. Moreover, we highlight recent advances showing that metabolic symbiosis can be modeled in vitro using a co-culture system. By employing this approach, it becomes apparent that oncogenes drive the onset of metabolic symbiosis by re-programming energy metabolism in the tumor microenvironment, via paracrine oxidative stress.

These findings have important implications for achieving the goals of personalized medicine and for designing more effective approaches to anticancer therapy, with a focus on new, highly selective metabolic inhibitors.

Stromal Caveolin-1: A Biosensor of Autophagy in the Tumor Microenvironment

An absence or loss of stromal caveolin-1 (Cav-1) immunostaining is a new biomarker of poor clinical outcome in many different types of cancers, such as breast tumors and DCIS, gastric and prostate carcinomas, as well as in metastatic melanoma lesions.[57-68] In breast cancer patients, a loss or stromal Cav-1 is specifically linked to tumor recurrence, metastasis, drug-resistance, and overall poor survival (**Fig. 1**). More specifically, oxidative stress in cancer-associated fibroblasts leads to the lysosomal/autophagic digestion of Cav-1.[30] As such, a reduction or absence of Cav-1 is a sensitive biomarker of oxidative stress, autophagy/mitophagy, and aerobic glycolysis, in the tumor stroma.[22,34]

Importantly, the prognostic value of stromal Cav-1 in breast cancer patients has now been independently validated in 7 different countries worldwide.[57-68]

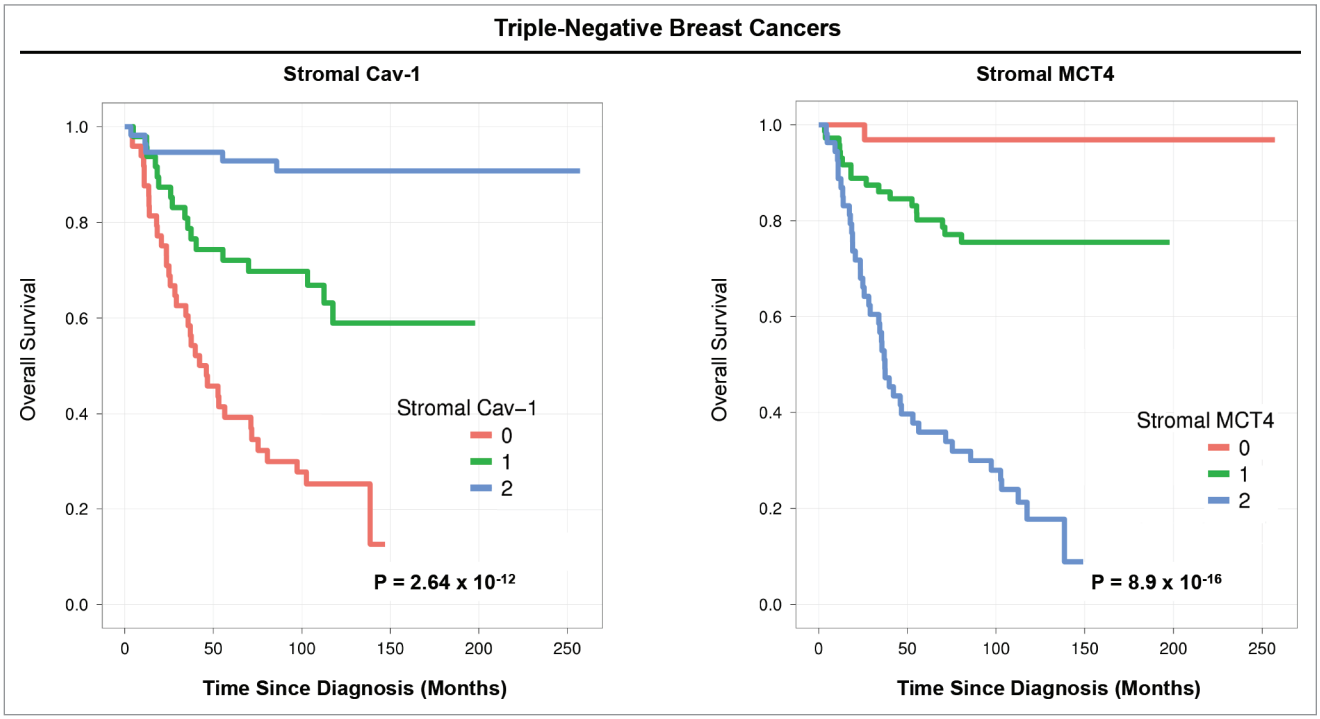

Figure 1. Kaplan–Meier analysis of overall survival, using stromal Cav-1 and mct4 to predict clinical outcome. (**A**) TMA containing a cohort of 185 triple-negative breast cancer patients, with over 20 y of clinical follow-up data, was subjected to immunostaining with antibodies directed against Cav-1 and MCT4. Then, the expression levels of these two protein biomarkers were scored in the tumor stroma. Note that loss of Cav-1 and overexpression of MCT4 are strictly associated with poor clinical outcome. In contrast, patients with high stromal Cav-1 and absent MCT4 show >90% survival at >20 years post-diagnosis. Reproduced, with permission, from reference 70.

Stromal MCT4: A Biosensor of Oxidative Stress, Glycolysis, and Mitochondrial Dysfunction

Similar to what we have previously observed for Cav-1, MCT4 is new marker of oxidative stress in tumor-associated fibroblasts.[55,56] For example, in head and neck cancers, MCT4 is a specific marker of cancer-associated fibroblasts, but it does not label normal fibroblasts.[69] Furthermore, in triple-negative breast cancers, stromal MCT4 expression is a strong predictor of poor clinical outcome.[70] In this patient cohort, loss of stromal Cav-1 was directly correlated with elevated levels of stromal MCT4 expression and poor survival in triple-negative breast cancer (**Fig. 1**).[70]

Functionally, MCT4 mediates the cellular export of L-lactate and ketones from glycolytic cells. Interestingly, MCT4 is highly upregulated under conditions of hypoxia and/or oxidative stress and is a HIF1-α target gene. Thus, MCT4 functions as a new biomarker of oxidative stress, glycolysis, and mitochondrial dysfunction in the tumor microenvironment.

Epithelial MCT1: A Marker of Cell Proliferation, Mitochondrial Power, and Stemness

Previously, we have presented experimental evidence that a "lactate shuttle" can also exist in human cancer tissues.[45,55,56,69] Under these conditions, tumor-associated stromal cells express MCT4 and release high-energy mitochondrial fuels (such as L-lactate and ketones) into the tumor stroma. In contrast, tumor cells upregulate MCT1, so they can efficiently import these mito-fuels to use as fuel in the TCA cycle and for OXPHOS in proliferative cancer cells. This form of metabolic-coupling may then allow cancer cells to successfully engraft in pre-clinical animal models, by the metabolic rewiring of their microenvironment.

MCT1 is also a new biomarker of mitochondrial activity and mass, and its expression levels correlate with high proliferation rates in vivo, as we have recently demonstrated.[69] More specifically, Ki-67 expression and MCT1 staining are directly linked in both normal mucosa, and head and neck cancer tissues. Also, Ki-67 and MCT1 are both well expressed in the basal stem cell compartment of normal mucosa, suggesting that MCT1 may be a new marker of "stemness" in epithelial cells.[69]

Exploring the Transition to Malignancy: Modeling Metabolic Symbiosis by Co-Culturing Normal and Oncogene-Transformed Epithelial Cells with Fibroblasts

Recently, we employed a new cell system, to study the potential metabolic consequence of oncogenic stress on the tumor microenvironment.[71] For this purpose, we used the HaCaT keratinocyte cell system, which consists of an isogenic set of "normal" and oncogenically transformed epithelial cell lines. In this context, the behavior of normal HaCaT cells was directly compared with transformed HaCaT cells, which harbor the overexpression of activated oncogenes, such as H-Ras (G12V) or NFkB (p65 subunit).

Briefly, normal and transformed HaCaT cells were co-cultured with immortalized human fibroblasts to determine the systemic effects of oncogenes on adjacent stromal cells. Metabolic parameters, such as ROS production/oxidative stress and glucose utilization, were quantitated using sensitive fluorescent probes. As a complementary approach, we also followed the expression of a panel of protein biomarkers, which reflect the onset of metabolic symbiosis (Cav-1, MCT4, and MCT1).[71]

Surprisingly, epithelial oncogene activation was indeed sufficient to trigger the cancer-associated fibroblasts phenotype, with a loss of stromal Cav-1 and the upregulation of stromal MCT4 expression (**Fig. 2**). These fibroblasts also showed increased ROS production and elevated glucose uptake, indicative of a shift toward glycolytic metabolism. Thus, we concluded that oncogenes drive the metabolic reprogramming of cancer-associated fibroblasts via oxidative stress[71] In accordance

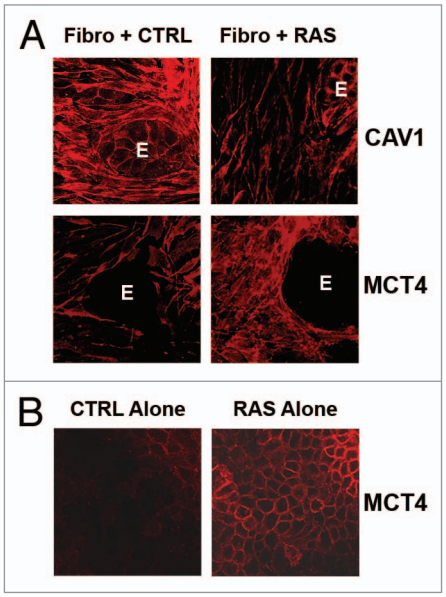

Figure 2. Epithelial oncogenes induce the cancer-associated fibroblast phenotype, in adjacent normal fibroblasts. Cav-1 and MCT4 as stromal biomarkers. (**A**) HaCaT cells (control [CTRL] vs. Ras-transformed [RAS]) were co-cultured with stromal fibroblasts. Then, the expression of Cav-1 and MCT4 was monitored by immunostaining. Note that Ras-transformed HaCaT cells specifically downregulate Cav-1 and upregulate MCT4 in adjacent fibroblasts, effectively functioning as reporters of the transition to malignancy in cancer cells. E, epithelia. (**B**) HaCaT cells (CTRL and RAS) were also cultured alone for comparison. Note that MCT4 is upregulated in Ras-transformed cells when they are cultured alone, but then downregulated when they are co-cultured with fibroblasts (as in **A**). Reproduced and modified, with permission, from reference 71.

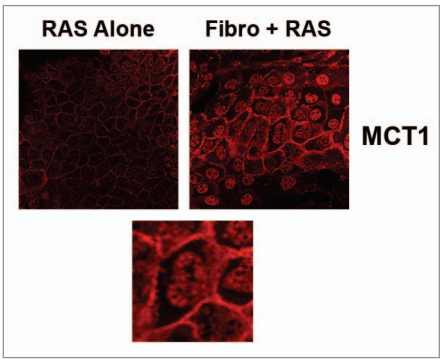

Figure 3. Fibroblasts induce the expression of MCT1 in epithelial cancer cells to facilitate metabolic symbiosis. HaCaT–Ras cells were cultured alone (left) or co-cultured with fibroblasts (right) and then subjected to immunostaining with antibodies directed against MCT1. Note that co-culture with fibroblasts induces the expression of MCT1 in Ras-transformed epithelial cells. Thus, co-culture of Ras-transformed cells with fibroblasts induces reciprocal metabolic reprogramming, leading to metabolic symbiosis. Reproduced and modified, with permission, from reference 71.

with this notion, treatment with N-acetyl-cysteine (NAC), a powerful antioxidant, was sufficient to reverse or prevent the cancer-associated fibroblast phenotype induced by activated oncogenes.

Most importantly, these changes in metabolic parameters and protein biomarkers were not induced by normal HaCaT cells. These findings provide the necessary proof-of-concept that stromal Cav-1 and MCT4 can be used as sensitive "biosensors", to monitor the transition to malignancy, both in vitro and in vivo.[71]

In addition, under these conditions, MCT1 was selectively upregulated in epithelial cancer cells, during co-culture with fibroblasts (**Fig. 3**). As such, it appears that oncogenes drive the establishment of a "lactate shuttle" and metabolic symbiosis, to enable the anabolic growth of tumor cells.

Virtually identical results were obtained with 2 distinct onco-proteins (RAS and NFkB), directly showing that oxidative stress and inflammation converge on the stromal compartment, leading to glycolytic metabolism in the tumor microenvironment (**Fig. 4**).

As a consequence of these findings, we should begin to consider stromal Cav-1 and MCT4 as new metabolic targets for drug development, as they are very specific biomarkers of the catabolic tumor-associated fibroblast phenotype.[71] Importantly, many diverse oncogenic stimuli (RAS, NFkB, TGF-β, loss of BRCA1, ethanol exposure, and ROS/hydrogen peroxide) all induce a common metabolic response in the tumor stroma,[20,21,56,72,73] which then dramatically changes the expression levels of both Cav-1 and MCT4 (**Fig. 5**). These studies directly support the "seed and soil" hypothesis, which was initially proposed over 100 years ago now by Stephen Paget.[74-77]

BRCA1 Loss and the Transition to Malignancy: Modeling Metabolic Symbiosis in Hereditary Breast and Ovarian Cancers

BRCA1 is a tumor suppressor gene which has several key functions, such as DNA repair and transcriptional regulation, as well as the modulation of cell cycle progression.[78] Mutations in the BRCA1 gene dramatically increases a woman's risk for the development of both breast and ovarian cancers. More specifically, women carrying a BRCA1 mutant allele have a >60% lifetime risk of breast cancer and a >40% lifetime risk of ovarian cancer.[79,80] BRCA1 mutations prevent protein production,[81] and BRCA1-mutated breast cancers show an absence of nuclear expression, which is associated with a poor prognosis.[82,83] Phenotypically, BRCA1-deficient breast cancers are usually high-grade, aggressive and triple-negative, based on gene expression studies and/or immunostaining of paraffin sections.[84-86] BRCA1 loss of expression also occurs commonly in sporadic breast cancers, secondary to epigenetic changes, and is often observed in triple-negative or basal-like tumors.[80,87-94] As a consequence, loss of BRCA1 protein function may also be a critical driver in both sporadic and familial breast cancers.[95,96]

Recently, we studied the metabolic effects of BRCA1 loss of function on the tumor microenvironment.[20] To recapitulate the tumor stroma, we developed a co-culture model in vitro. Briefly, HCC.1937 breast cancer cells, which harbor mutations that completely inactivate BRCA1 protein expression (BRCA1-null), were co-cultured with hTERT-immortalized stromal fibroblasts.[20]

Interestingly, HCC.1937 cells drive ROS production in adjacent fibroblasts,

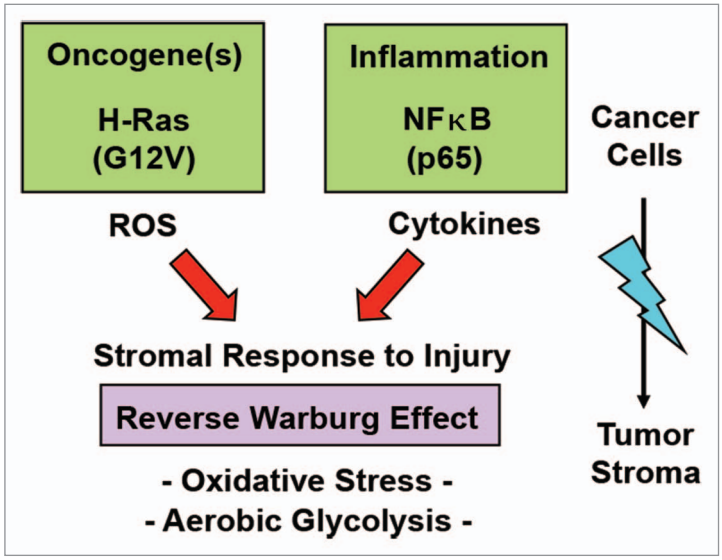

Figure 4. Oncogenes drive oxidative stress and glycolysis in the tumor microenvironment. Summary illustrating that 2 divergent oncogenes (RAS and NFkB) use ROS production and cytokines (inflammation) to induce oxidative stress and glycolysis in adjacent cancer-associated fibroblasts ("the reverse Warburg effect"). Thus, oncogenes act at a distance, to metabolically reprogram the tumor microenvironment.

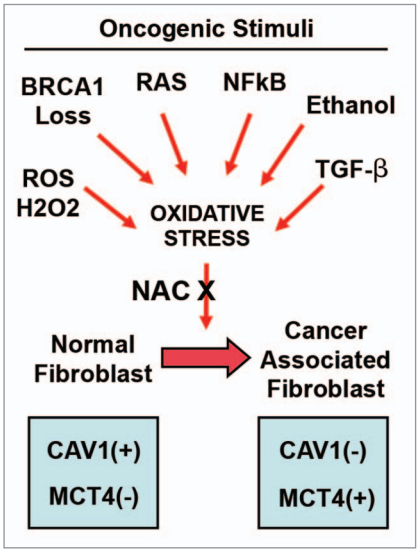

Figure 5. Diverse oncogenic stimuli induce the cancer-associated fibroblast phenotype via oxidative stress. Diagram illustrating that diverse oncogenic stimuli (RAS, NFkB, TGF-β, BRCA1 loss, ethanol exposure, ROS/hydrogen peroxide) all induce oxidative stress in the tumor microenvironment. This, in turn, promotes the catabolic cancer-associated fibroblast phenotype, resulting in a loss of Cav-1 and an increase in MCT4 expression. Treatment with N-acetyl-cysteine (NAC), a powerful antioxidant, is sufficient to reverse or prevent the cancer-associated fibroblast phenotype induced by these divergent oncogenic stressors.

and induce the cancer-associated fibroblast phenotype, with the stromal loss of Cav-1 and MCT4 upregulation.[20] Remarkably, this CAF phenotype was suppressed either by genetic replacement of the BRCA1 gene in epithelial cancer cells, or by treatment with powerful antioxidants, such as NAC (**Fig. 6A**).

Human breast cancer samples harboring BRCA1 mutations (9 out of 10 examined) also showed a loss of stromal Cav-1 and the upregulation of MCT4, as well as striking mitochondrial staining with TOMM20, a marker of mitochondrial mass (**Fig. 6B**). Therefore, BRCA1 loss of function drives ROS generation in both mammary epithelial cells and adjacent stromal fibroblasts. This paracrine oxidative stress then promotes the onset of a glycolytic stromal phenotype with metabolic symbiosis, which is reflected by decreased Cav-1 and increased MCT4 expression.[20]

Quantitatively similar results were also obtained with the BRCA1-deficient ovarian cancer cell line, namely UWB1.289 cells.[21] These BRCA1-null ovarian cancer cells produced large amounts of ROS. This, in turn, induced oxidative stress and catabolic metabolism in neighboring stromal fibroblasts (glycolysis, autophagy, and mitophagy).[21] These functional changes reflected the onset of the CAF-phenotype and were strictly associated with MCT4 upregulation and Cav-1 loss of expression (**Fig. 7A and B**), which are markers of "metabolic symbiosis" within the tumor microenvironment. In these UWB fibroblast co-cultures, the CAF phenotype was suppressed by either genetic replacement of the BRCA1 gene in ovarian cancer cells, or by treatment with powerful antioxidants, such as NAC.[21]

ROS production in BRCA1-null ovarian cancer cells also resulted in the paracrine induction of an inflammatory phenotype in adjacent cancer-associated fibroblasts, with the strong activation of an NFkB–luciferase reporter (**Fig. 8**).[21] ROS production and oxidative stress are known activators of NFkB, consistent with the idea that redox signaling promotes an inflammatory phenotype, via the activation of innate immunity.

Taken together, these functional studies suggest that cancer prevention trials, with antioxidants and/or anti-inflammatories, may be warranted in women with a genetic history of familial BRCA1 mutations.[20,21] This novel chemo-prevention approach would be expected to inhibit "metabolic symbiosis" in high-risk BRCA1 patients and reverse the cancer-associated fibroblast phenotype, essentially cutting off the "fuel supply" to cancer cells during tumor initiation.

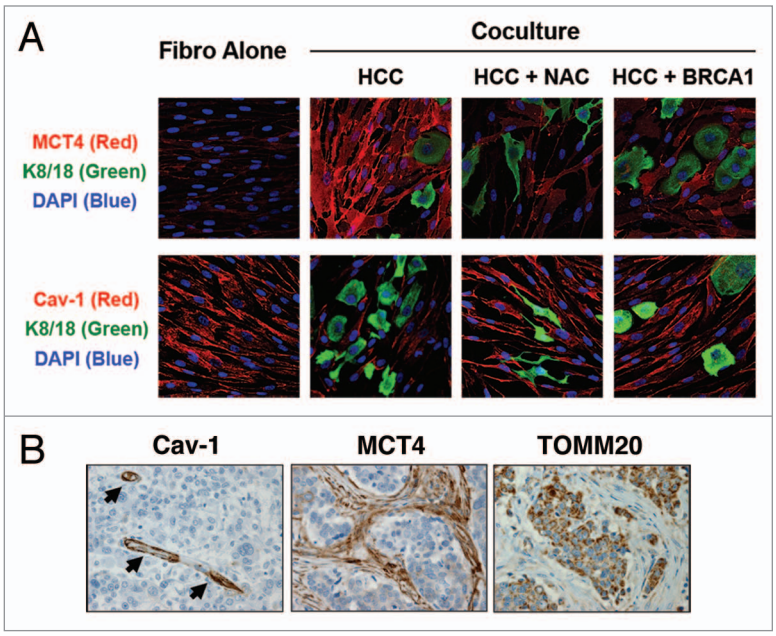

Figure 6. BRCA1-deficient breast cancer cells induce the cancer-associated fibroblast phenotype. (**A**) BRCA1-deficient HCC cells were co-cultured with hTERT-immortalized fibroblasts. Then, expression of Cav-1 and MCT4 was monitored by immunostaining. Note that HCC cells drive a loss of stromal Cav-1 and the induction of stromal MCT4. Importantly, this CAF-phenotype was suppressed either by genetic replacement of the BRCA1 gene in the epithelial cancer cells, or by treatment with NAC, a powerful antioxidant. (**B**) Human breast cancer samples harboring BRCA1 mutations (9 out of 10 examined) also show a loss of stromal Cav-1 and the upregulation of MCT4, as well as strong mitochondrial staining with TOMM20, a marker of mitochondrial mass. For Cav-1 immunostaining, arrowheads point at blood vessels, which do not show a loss of Cav-1, in contrast to adjacent stromal fibroblasts. Images from one representative patient are shown. Reproduced and modified, with permission, from reference 20.

"Fibroblast Addiction": A New Therapeutic Target for Cancer Therapy and the Prevention of Drug Resistance

The desmoplastic tissue reaction, or fibroblast-overgrowth, is a generalized response to injury, but can also occur during tumor initiation and metastasis. As such, the desmopastic reaction is a true wound-healing response. However, the exact role of desmoplasia or tissue fibrosis in tumor initiation and progression still remains unknown.

Our recent data suggest that the desmoplastic reaction could actually help allow cancer cells to survive during oncogene activation and to overcome the cellular stress associated with malignant transformation. For example, we and others recently showed that catabolic fibroblasts inhibit oxidative stress in epithelial cancer cells.[71,97] During metabolic symbiosis, cysteine (Cys) produced in stromal cells is transferred to cancer cells, where it is converted to glutathione (gamma-Glu-Cys-Gly), a powerful antioxidant.[97] This, in turn, functionally protects cancer cells against oncogenic stress,[71] which would otherwise induce cell death, via various stress-related mechanism(s), including apoptosis, autophagy, and/or senescence (**Fig. 9**). Previous studies have also shown that this mechanism may confer drug resistance to anti-estrogens and other chemotherapeutic agents, in epithelial cancer cells.[23,24,31,33]

These findings suggest that primary cancer cells are "addicted to fibroblasts"

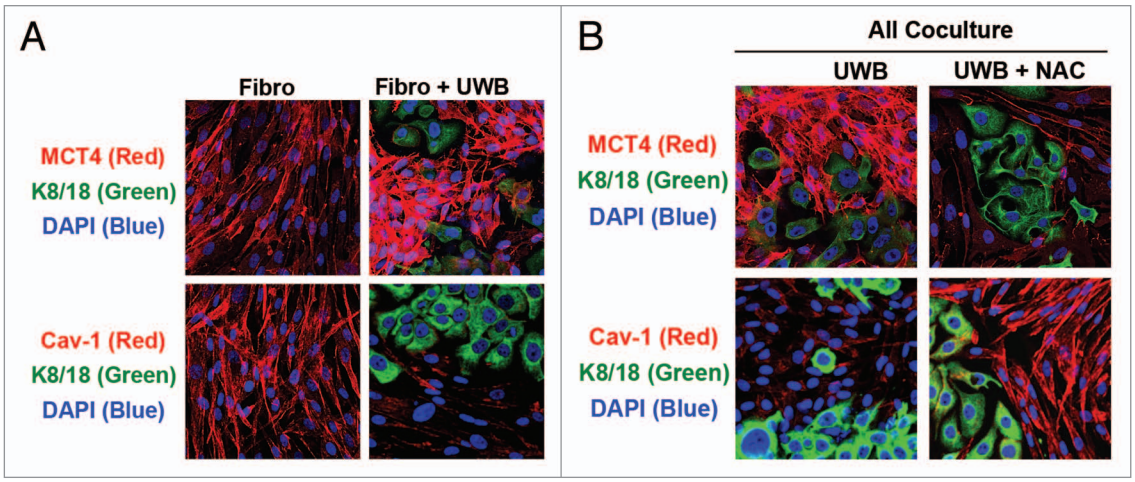

Figure 7. BRCA1-deficient ovarian cancer cells induce the cancer-associated fibroblast phenotype. (**A**) BRCA1-deficient UWB cells were co-cultured with hTERT-immortalized fibroblasts. Then, the expression of Cav-1 and MCT4 was monitored by immunostaining. Note that UWB cells drive a loss of stromal Cav-1 and the induction of stromal MCT4. (**B**) Importantly, this CAF-phenotype was suppressed by treatment with NAC, a powerful antioxidant. Genetic replacement of the BRCA1 gene in the epithelial cancer cells also suppressed the CAF-phenotype (not shown). Reproduced and modified, with permission, from reference 21.

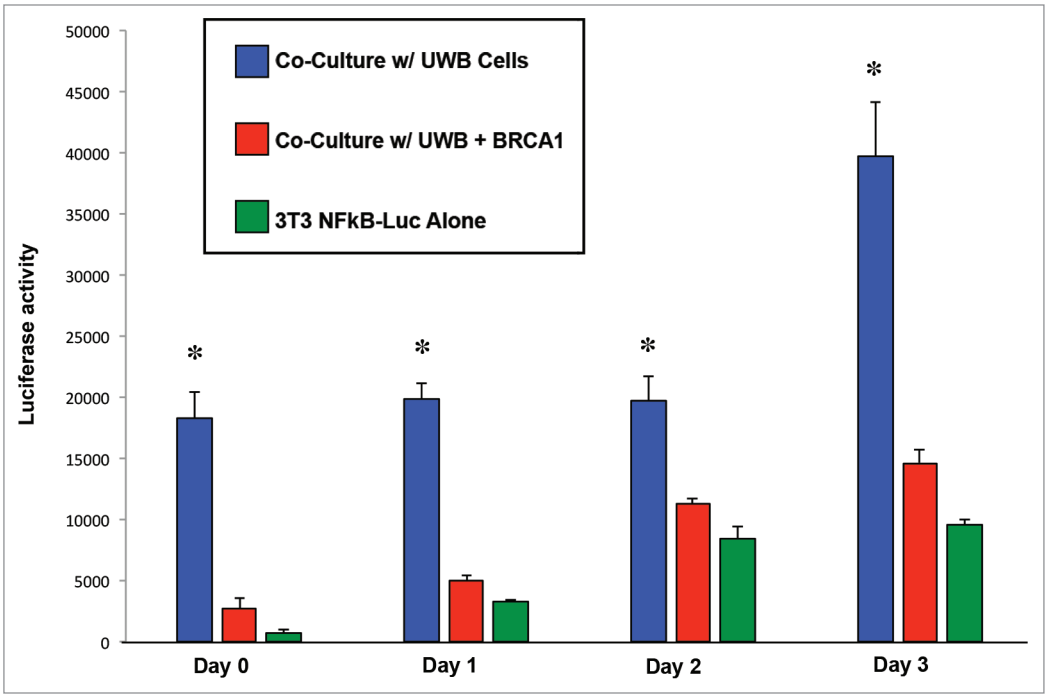

Figure 8. BRCA1-deficient ovarian cancer cells induce an inflammatory phenotype in adjacent stromal fibroblasts. BRCA1-deficient UWB cells were co-cultured with NIH-3T3 fibroblasts, harboring an NFkB–luciferase reporter, to measure the activation of an inflammatory phenotype. Note that co-culture with BRCA1-deficient UWB cells activates NFkB-mediated gene transcription, in adjacent stromal fibroblasts. Furthermore, this pro-inflammatory phenotype was rescued by recombinant expression of the wild-type BRCA1 gene in UWB cells. The basal state of NFkB activation in NIH-3T3 fibroblasts cultured alone is shown for comparison. Day 0 actually represents 24 h of co-culture. Reproduced and modified, with permission, from reference 21.

for their survival, and that separating them from stromal fibroblasts, may actually catalyze the death of cancer cells. These data could help explain why it is so difficult to generate new "immortal" cancer cell lines from patient samples, as one of the first steps involves the purification of epithelial cancer cells away from stromal fibroblasts.[98]

Thus, new therapies could be developed to functionally target "fibroblast addiction". If stromal cells are therapeutically targeted, then an expected result would be acute oncogene-induced stress in epithelial tumor cells, driving the starvation and/or death of cancer cells. This acute stress would likely result in tumor regression.

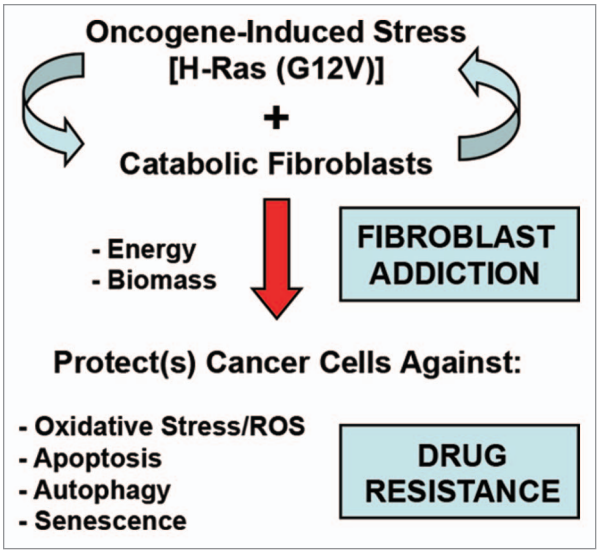

Figure 9. Fibroblast addiction: Fibroblasts alleviate oncogenic stress in epithelial cancer cells. Catabolic fibroblasts provide high-energy fuels and precursors for biomass to adjacent cancer cells. As a consequence, fibroblasts protect cancer cells against stress by reducing ROS production, apoptosis, autophagy, and senescence in epithelial cancer cells. Experimental evidence indicates that this "fibroblast addiction" also confers drug resistance to anti-estrogens and other chemotherapeutic agents by promoting oxidative mitochondrial metabolism in epithelial tumor cells.

Conclusions and Future Directions

In summary, we conclude that oncogene activation (RAS, NFkB, TGF-β) and/or tumor suppressor loss (BRCA1) both have very similar functional effects on adjacent stromal fibroblasts, driving the initiation of metabolic symbiosis and the cancer-associated fibroblast phenotype. As such, new therapeutic strategies that metabolically uncouple oxidative cancer cells from their glycolytic stroma, could be used to target this "fibroblast addiction" in both primary and metastatic tumor cells.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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